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TITLE: Training Program in Biostatistics for Breast Cancer Research

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RAHutte 8/12/96  
PI - Signature Date

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## INTRODUCTION

The purpose of this training program in biostatistics for breast cancer research is to provide biostatisticians with the requisite scientific knowledge to understand current issues in breast cancer research, and training in statistical and epidemiological techniques and research methodology related to breast cancer. The training leads to the doctorate of philosophy in biostatistics. The methods of training include formal course work in biostatistics, epidemiology and biology related to breast cancer, interdisciplinary seminars on current research and biostatistical topics in breast cancer research, and mentored research in collaboration with biostatistics faculty and breast cancer investigators.

The initial report summarizing the activities in the second year of the this training grant was rejected. This revised report updates the activities of this training grant in the second year as suggested by the reviewer(s) of the initial report. Additions or modifications to the initial report have been highlighted by italicization.

## TRAINING IN BIOSTATISTICS

*To achieve the stated objectives of this training program in biostatistics for breast cancer research, the following steps have been and are being taken:*

- *To obtain requisite scientific knowledge to understand current issues in breast cancer research, the trainees are required to regularly attend the relevant talks from "Cancer Center Grand Rounds", "Cancer Biology Seminars", and "Statistical Methods in Cancer Research". The list of topics and speakers for these seminar series for the academic years 1995-1996 and 1996-1997 are attached in Appendix 1.*
- *For training in statistical and epidemiological techniques and research methodology relevant to and necessary for breast cancer research, the trainees are advised and required to take (1) theoretical courses in statistics and probability from the Departments of Statistics and Biostatistics, (2) relevant methods and applied courses in biostatistics from the Department of Biostatistics, and (3) courses in cognate areas proposed in the original grant applications from the Departments of Epidemiology and Environmental and Industrial Health and from other Departments in the Schools of Public Health and Medicine.*
- *The trainees have been and are involved in mentored collaborative research in breast cancer with the breast cancer researchers from the University of Michigan Comprehensive Cancer Center (UMCCC) and with the faculty from the Department of Biostatistics.*

## STATEMENT OF WORK

*During year 2 of the training program, we have performed the following work as planned in the Statement of Work of the original application:*

- *Task 5: Ms. Kester was nominated as candidate by the Department of Biostatistics and selected by the Steering Committee.*
- *Task 6: Active training areas, Prevention and Therapeutic Clinical Trials, was evaluated in terms of the progress made by the trainees with electronic communications to the Steering Committee members.*
- *Task 7: The progress made by the trainees were presented to the Steering Committee. Also a slate of new trainees, Messrs. Lang Li, Rajat Mukherjee and Gong Tang, were nominated by the Department of Biostatistics and approved by the Steering Committee. At this Steering Committee meeting, the proposal to supplement the stipend level from 35% to 50% using the UMCCC's Biostatistics Core funds was approved. (See the New Initiatives.)*

*The times of these tasks have varied slightly from time to time.*

## CHANGE IN LEADERSHIP

In September of 1996, KyungMann Kim, Ph.D., joined the University of Michigan School of Public Health as Associate Professor (with tenure) of Biostatistics and Director of Biostatistics Core of the University of Michigan Comprehensive Cancer Center. As indicated in the annual report covering the period from July 11, 1994 to July 10, 1995, the Principal Investigator was changed from Dr. Little to Dr. Kim in February of 1996. This was an expected change, considering the nature of Dr. Kim's involvement with and responsibilities at UMCCC, and this change obviously makes the training program in biostatistics for breast cancer research much stronger for the same reasons.

### Rationale for Dr. Kim Assuming the Position of PI for the Grant

*The second reviewer criticized the departure of Dr. Little as principle investigator, stating that there was no indication in the (1994-95 annual report) that Dr. Little would be departing as PI, and stating that an explanation for his withdrawal as the PI for the program was needed.*

*When the grant was written, Dr. Little and Dr. Bromberg were named as co-principal investigators to provide coverage of the Biostatistics and Cancer research activities of the grant. Dr. Bromberg involvement was as Director of the Biostatistics Core in the Cancer Center, and was essential to ensure access to Breast Cancer researchers and facilitate cancer training*

for the trainees. However, she had a junior research appointment in the Biostatistics Department (Assistant Research Scientist), and as such had no involvement in teaching formal Biostatistics courses, her research was mainly collaborative in nature, and she had no role in Ph.D. student dissertation direction. Dr. Little, the incoming Chair of the Department, was included as a co-principal investigator to provide academic leadership, and a connection with the formal didactic program in the Biostatistics Department.

In the 1994-95 Annual Report for the Training Grant, the impending appointment of Dr. Kim as Director of the Biostatistics Core in the Cancer Center was announced, and it was stated that "it is expected that Dr. Kim will assume a leadership role in this training grant when he assumes his new position at Michigan". In the meantime, the appointment of Dr. Kim as Principal Investigator for the Grant was approved by the U.S. Army project management.

Dr. Kim is highly appropriate and qualified to lead both the Breast Cancer research and Biostatistics components of this training grant. As Director of the Biostatistics Core, he leads biostatistical activities in the Cancer Center, which serves as the administrative focus for nearly all cancer research at the University of Michigan. This position has been upgraded since Dr. Bromberg's tenure by substantial additional funding in the Cancer Center Biostatistics Core, and the commitment of a tenured faculty position. Unlike Dr. Bromberg, whose research appointment did not involve teaching and dissertation direction, Dr. Kim is associate professor with tenure in the Department of Biostatistics, has a strong independent research program in cancer biostatistics, has served as principal investigator on NIH grants, and teaches graduate-level courses for the Department—he is currently teaching a course in clinical trials. Dr. Kim is very familiar with the objectives of the training grant and fully committed to its current and future development.

With Dr. Kim's recruitment, there was no longer the need for split leadership of this small training program, as he is clearly appropriate to lead all aspects of the activity. Dr. Little remains a member of the Steering Committee for the Training Grant, and as Chair of the Department has an overarching responsibility for biostatistics graduate student training. However, since he is not now involved in Cancer Center activities, he is no longer well-positioned to provide the cancer research component that is the key to the training grant's success.

The reviewer stated that "it is not at all clear or justified that the training grant ... be solely an arm of the UMCCC, rather than administered through a broader-based Biostatistics Department. There is more to breast cancer research than that reflected in the biostatistics core of the UMCCC. When Dr. Little/Dr. Bromberg were the principal investigators, there was a broad-based breast cancer potential."

As noted above, Dr. Kim is a full tenured member of the Biostatistics Department, and the grant continues to be administered in the Biostatistics Department. Practically all breast cancer research is conducted by researchers associated with the UMCCC, and with the expansion of the UMCCC Biostatistics Core since Dr. Kim's arrival, the broad-based breast cancer potential of the grant has in fact increased, not contracted.



## DESCRIPTION OF TRAINEES

With the guidance and approval of the Steering Committee, one new highly-qualified trainee, Ms. Monica Kester, was appointed to the training program for the 1995-96 academic year. Ms. Kester was one of the top applicants for the Ph.D. program in Biostatistics for the 1995-1996 academic year. She entered the program with a BA in Mathematics, Magna cum Laude, from the State University of New York at Geneseo and an MA in Statistics from Yale University. Hence, during the 1995-1996 academic year, there were three doctoral students, Messrs. Daowen Zhang and Hua-Yun Chen and Ms. Kester, from the Biostatistics Department supported on this training program in biostatistics for breast cancer research.

Since becoming a doctoral candidate in July of 1995, Mr. Zhang has been working with Drs. Xihong Lin and Mark Becker on longitudinal categorical data and has made a lot of progress toward completing his thesis. He is expected to complete his dissertation during the upcoming academic year. *A letter from Dr. Lin summarizing Mr. Zhang's progress is attached in Appendix 2.*

Mr. Chen has continued to excel in course work during the last academic year. *He has passed part II qualifying exam in September of 1996, and has advanced to become a doctoral candidate.* He has been *mentored by* and working with Dr. Little on problems with missing data in covariates and has been making steady progress, while still taking required course work. Also he has worked with Ms. Strawderman and Dr. Little on a missing-data problem involving data from a breast cancer clinical trial. *A letter from Dr. Little summarizing Mr. Chen's progress is attached in Appendix 2.*

Ms. Kester sat in on a number of statistical consulting sessions at the UMCCC Biostatistics Core. She was also given the opportunity to attend the Annual Meeting of the Society for Clinical Trials *with funding from the Biostatistics Core of the Cancer Center.* For the summer she worked at Bristol-Myers Squibb in Wallingford, Connecticut as Intern on cancer clinical trial projects. She continues to excel in her course work in biostatistics (*with cumulative GPA of 7.78 out of 8*), and she has elected to take cognates in genetics in public health. *A letter from Dr. Kim summarizing Ms. Kester's progress is attached in Appendix 2.*

All three trainees have regularly attended Cancer Center's Grand Rounds, and are becoming involved in breast cancer research. *The list of topics and speakers for these seminar series are attached in Appendix 1, along with the list for the new seminar series in "Statistical Methods for Cancer Research".* Unfortunately, however, both Messrs. Chen and Zhang have elected to go off the training program at the end of the academic year 1995-1996. For Mr. Zhang this was due to personal reasons: *He has elected to work with Dr. MaryFran Sowers of the Department of Epidemiology on a four-year multi-center longitudinal study on breast cancer survivors, which is currently under review for funding from the Department of Defense Breast Cancer Research Program.*

In the case of Mr. Chen, both the new PI, Dr. Kim, and the previous PI, Dr. Little, felt that it was more appropriate for him to work with Dr. Little with support from his NSF grant on missing data problems. *Despite the fact that Mr. Chen has gone off the training program,*



*his thesis research was motivated by a data set involving breast cancer survivors he analyzed while on the training program. Mr. Chen has made an impressive progress so far with one finalized manuscript entitled "Proportional Hazards Regression with Missing Covariates".*

*The updated summaries of training activities of the trainees for the 1995-1996 academic year is attached in Appendix 3.*

At the Steering Committee meeting in July 1996, it was decided to award a traineeship to two incoming students, Messrs. Mukherjee and Tang, *commencing with the academic year 1996-1997* and to one additional incoming student, Mr. Li, *commencing with the winter term. They have all entered the Ph.D. program in Biostatistics in the Fall of 1996. The appointment for all the trainees will be continuous for the duration of the funding.*

Mr. Mukherjee has a bachelor's degree (*with First Class designation for grade*) in Operations Research and Statistics from Calcutta University in India and a MS degree in Statistics (*with GPA of 3.9 out of 4*) from the Bowling Green State University in Toledo, Ohio. *Although he does not have a specific biology background, which is typically the case for students in any biostatistics programs, he was involved in a project on Health, Sanitation and Air Pollution in Calcutta, India for which he had to sit in for an environmental science and an ecology class.* Mr. Tang has a BA in Mathematics (*with GPA of 3.8 out of 4*) from Beijing University in China and a MA in Mathematics (*with GPA of 3.7 out of 4*) from Johns Hopkins University in Baltimore. Mr. Li has a BS in Mathematics (*with GPA of 92.9 out of 100*) from Wuhan University in China and a MS in Statistics (*with GPA of 3.91 out of 4*) from the University of New Mexico in Albuquerque. All three new trainees expressed a keen interest in applications of Biostatistics to general cancer research in their application.

### **Concerns for Commitment in Breast Cancer Research**

*Considering the limited pool of applicants with interests in cancer research, our strategy is to appoint as the trainees for this program those applicants with the best qualification for admission to the Department of Biostatistics and with any interest in cancer research. There is hardly any difference between the biostatistical training in breast cancer research and the biostatistical training in general cancer research.*

*With Dr. Kim's tenured appointment in the Department of Biostatistics and his leadership in the Cancer Center, the training program provides an excellent setting for high quality training in biostatistics for cancer research generally and for breast cancer research specifically. Excellent training in biostatistics for breast cancer research cannot and should not be pigeonholed. The orientation for breast cancer research can only be nurtured with exposure to interesting collaborative research projects, which is being done as summarized in the New Trainee Activities discussed below.*

*The current level of stipend from the training grant is not sufficient for these trainees to make a living, and this is one of the reasons why former trainees chose to go off the grant. With the excellent general training in biostatistics provided by the Department, the breast cancer*

*emphasis is provided by exposure to projects in breast cancer research through collaborative efforts. The supplement from the UMCCC Biostatistics Core provides an incentive and a mechanism to get the trainees directly involved in the breast cancer research projects in the Cancer Center.*

## TRAINING PERSONNEL

The UMCCC Biostatistics Core has the following statistician staff: KyungMann Kim, Ph.D., Director of Biostatistics; Daniel Normolle, Ph.D., Senior Research Associate; Myla Strawderman, M.S., Research Associate II; and Songbai Wang, M.S.P.H., Research Associate I. With Dr. Kim assuming the leadership of the training program as PI, the role of the UMCCC Biostatistics Core has already expanded. (See the New Initiatives in the section on OTHER ACTIVITIES).

*This in no way implies that the training grant be solely an arm of the Cancer Center. On the contrary, the training grant is administered solely by the Department of Biostatistics. Having Dr. Kim who is tenured associate professor in the Department of Biostatistics as PI of this training program has strengthened the training program because of his dual role in the Department of Biostatistics and the Cancer Center.*

In addition to the mentors from the UMCCC Breast Oncology Program and from the Biostatistics Department, all four statisticians from the UMCCC Biostatistics Core play an active role in supervising the trainees and in providing guidance and supervision for interaction with the UMCCC breast cancer investigators.

## BUDGET MATTERS

*The following table summarizes the budget expenditures for this training grant:*

<i>Category of Expenditures</i>	<i>Year 1</i>		<i>Year 2</i>
	<i>7/11/94-7/10/95</i>	<i>7/11/95-7/10/96</i>	
<i>Stipends</i>	<i>10,694</i>		<i>21,252</i>
<i>Tuition and Fees</i>	<i>19,861</i>		<i>30,591</i>
<i>Health Care</i>	<i>4,542</i>		<i>5,734</i>
<i>Total</i>	<i>35,097</i>		<i>57,577</i>
<i>Average funding per trainee</i>	<i>17,548</i>		<i>19,192</i>

*The next table shows the actual cost of supporting one trainee in the program for 2 university terms from September to April of the following year:*

Category of Costs	Year 1		Year 2
	7/11/94-7/10/95	7/11/95-7/10/96	
Stipend at 35% level	6,866		7,071
Non-resident Tuition and Fees	16,978		18,214
Total†	23,844		25,286

† The total does not include the cost of trainee's health care insurance.

Obviously, the funding level for this training program which is \$20,000 per trainee per academic year does not meet the trainees' needs. To maintain active and continuous participation in the grant, we also seek to provide support for the trainees during the Spring and Summer terms.

## OTHER ACTIVITIES

### Steering Committee

The steering committee met, in July 1996, to review the trainees' progress, evaluate nominees for future trainees, new initiatives for the training program, and consider grant activities.

We have rotated off two members of the Steering Committee, Drs. Chang and Merajver, and have added two new members, Dr. Penny Pierce of the School of Nursing and Dr. Thomas Chenevert of the Department of Radiation Oncology of the School of Medicine.

We have identified a new area of breast cancer cognate, *Psychosocial Aspects of Breast Cancer*. Dr. Pierce is a PI of a project, "Knowledge, Beliefs, and Preferences of African American Women Concerning Breast Cancer Treatment". In this project she is interested in identifying psychosocial domain of patients which affects their breast cancer treatment choice.

Dr. Chenevert is a PI of a project, "Rapid 4D MRI of Gad-DTPA Enhancement for Breast Lesion Characterization," funded by the Department of Defense Breast Cancer Research Program. The main objective of this project is to determine the diagnostic power of quantitative gadolinium-DTPA contrast enhancement rate constants in a prospective clinical imaging trial using a recently developed rapid 4-dimensional magnetic resonance imaging technique. With Dr. Chenevert, we can now provide strong training in one of the four original cognate areas, i.e., "Statistical Problems in Imaging Studies and the Screening and Detection of Breast Cancer".

### New Trainee Activities

Mr. Tang has been working on Dr. Pierce's project with mentorship from Drs. Kim and Pierce. Ms. Kester has been working on Dr. Chenevert's project with mentorship from

*Drs. Chenevert and Kim. Mr. Mukherjee has begun to work with Dr. Chang, former Steering Committee member, and Dr. John Ingold from William Beaumont Hospital in Royal Oak, Michigan on analysis of a breast cancer database of over 1,500 patients who were surgically operated on by Dr. Ingold with mentorship from Dr. Kim.*

## **New Initiatives**

The most significant new initiative is the plan to supplement trainees' stipend level from the current 35% to the regular 50% with partial funding from the UMCCC Biostatistics Core grant. This supplement in stipend will require trainees to actually work as a part time graduate student research assistants in the Biostatistics Core. The trainees will work on relevant breast cancer research projects with supervision of the UMCCC statisticians in the Biostatistics Core.

With the Fall term, there *has been* a biweekly working group seminar series in "Statistical Methods for Cancer Research". This will be used as a forum to visit new statistical research initiatives for breast cancer research in particular and for cancer research in general. *With the Winter term, this biweekly seminar series will alternate with a journal club for statistical issues in breast cancer research. A list of articles to be considered for review by the journal club is attached in Appendix 1.*

## **CONCLUSIONS**

The training program is maturing nicely with a meaningful progress, despite loss of two excellent trainees as we *have recruited* three new talented trainees for the third year of the grant. Especially, all three and the soon-to-be-fourth trainees are a lot more committed toward biostatistics for breast cancer research. In the future, this training program will play a more active important role in the further expansion and development of Biostatistical training and research activities in the Biostatistics Department.

Eventually we plan to develop a training program in biostatistics for cancer research for submission to the National Cancer Institute when the current training program from the Department of Defense terminates.

## **Appendix 1**

1. A list of topics and speakers for the Cancer Center's Grand Rounds
2. A list of topics and speakers for the Cancer Biology Seminars
3. A list of topics and speakers for the Statistical Methods for Cancer Research Seminars
4. A list of articles for the Journal Club for Statistical Issues in Breast Cancer Research

The University of Michigan  
Comprehensive Cancer Center Grand Rounds

**1995**

**January**

- |    |   |   |
|----|---|---|
| 13 | Rich Wahl, M.D.<br>Professor, Internal Medicine and Radiology<br>University of Michigan                             | "Tumor Targeted Radioactivity for<br>Cancer Diagnosis and Therapy"                              |
| 20 | C. Norman Coleman, M.D.<br>Professor and Chairman<br>Department of Radiation Oncology<br>Harvard Medical School     | "Improving the Results of Radiation<br>Therapy -- Understanding the Tumor<br>Micro Environment" |
| 26 | Eugene Woltering, M.D.<br>Chief, Section of Surgical Endocrinology<br>Louisiana State University School of Medicine | "Role of Somatostatin Analogues in<br>Tumor Growth and Angiogenesis"                            |

**February**

- |    |  |   |
|----|--|---|
| 10 | Richard Boland, M.D.<br>Professor of Internal Medicine<br>University of Michigan   | "Defective DNA Mismatch Repair in<br>Colorectal Cancer"   |
| 17 | Kevin Cooper, M.D.<br>Associate Professor, Dermatology<br>University of Michigan   | "Inflammatory and Immunologic U.V.<br>Injury Mechanisms: A Model for the<br>Acute Effects of a Complete Carcinogen" |
| 24 | Daniel Von Hoff, M.D.<br>Director, Research Cancer Therapy and<br>Research Center<br>The University of Texas Health Science<br>Center at San Antonio | "New Anti Cancer Agents with Significant<br>Clinical Activity"  |

**March**

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|----|--|--|
| 3  | Edison Liu, M.D.<br>Associate Professor, Medicine<br>University of North Carolina<br>UNC Lineberger Comprehensive Cancer Center  | "Protein Kinases in Human Breast Cancer"               |
| 10 | Joseph R. Bertino, M.D.<br>Chairman, Molecular Pharmacology and<br>Therapeutics<br>Sloan-Kettering Institute for Cancer Research | "Tumor Suppressor Genes and Drug<br>Resistance"        |
| 17 | Robert Livingston, M.D.<br>Professor of Medicine<br>Head, Division of Oncology<br>University of Washington School of Medicine    | "Dose Response and Dose Intensity<br>in Breast Cancer" |

The University of Michigan  
Comprehensive Cancer Center Grand Rounds

- |    |   |   |
|----|---|---|
| 24 | Laura Koutsky, Ph.D.<br>Associate Professor of Epidemiology<br>Center for AIDS and STDs<br>University of Washington | "Acquisition and Natural History of<br>Genital Papillomavirus Infections in<br>Women" |
| 31 | Chi Dang, M.D., Ph.D.<br>Director, Division of Hematology<br>John Hopkins University School of Medicine             | "Mechanisms of C-Myc Mediated<br>Neoplastic Transformation"                           |

**April**

- |    |   |  |
|----|---|--|
| 7  | Sen-itiroh Hakomori, M.D.<br>Professor & Scientific Director<br>Departments of Pathology and<br>Microbiology & Immunology<br>University of Washington | "Functional Roles of Glycosphingolipids<br>in Disease Progression"                         |
| 21 | John Reed, M.D., Ph.D.<br>Director, Oncogene and Tumor Suppressor<br>Gene Program<br>LaJolla Research Foundation                                      | "Bcl-2 and Chemo Resistance in Indolent<br>Non-Hodgkins Lymphomas and Other<br>Cancers"    |
| 28 | Ralph Reisfeld, Ph.D.<br>Head, Tumor Biology<br>Scripps Institute   | "Recombinant Antibody - Cytokine Fusion<br>Proteins: A New Approach for Cancer<br>Therapy" |

**May**

- |    |  |   |
|----|--|---|
| 5  | Ellen Vitetta, Ph.D.<br>Direcot, Cancer Immunobiology Center<br>U- Texas Southwestern Medical Center   | "Monoclonal Antibodies as Carriers of<br>Toxins and as Agonists in Cancer<br>Therapy" |
| 12 | Saraswati Sukumar, Ph.D.<br>Professor, Molecular Biology of Breast Cancer<br>The Salk Institute for Biological Studies                                   | "Genetic Analysis of Breast Cancer"   |
| 19 | Jay Berzofsky, M.D., Ph.D.<br>Chief, Molecular Immunogenetics and<br>Vaccine Research Section<br>Metabolism Branch, NCI<br>National Institutes of Health | "Designing Peptide Vaccines for Aids<br>and Cancer"                                   |
| 26 | Eileen White, Ph.D.<br>Professor, Biological Sciences<br>Rutgers University<br>Center for Advanced Biotechnology and Medicine                            | "Regulation of Apoptosis by Viral<br>Oncogene and Tumor Suppressor Genes"             |

**September**

- |   |  |  |
|---|--|--|
| 8 | Richard Fisher, M.D.<br>Professor of Medicine<br>Loyola University | "Management of Non-Hodgkins<br>Lymphoma" |
|---|--|--|



The University of Michigan  
Comprehensive Cancer Center Grand Rounds

- 15 Laurence Leichman  
Program Director  
Gastrointestinal Cancer Program  
Kenneth Norris Cancer Center  
"Molecular Determinants of the Response and Resistance in G.I. Malignancies"
- 22 Tyler Jacks, Ph.D.  
Assistant Investigator  
Howard Hughes Medical Center  
MIT Center for Cancer Research  
"Tumor Suppressor Gene Mutations in Mice"
- 29 Gerald Hanks  
Chairman  
Department of Radiation Oncology  
Fox Chase Cancer Center  
"Strategies for Improving Outcome of Prostate Cancer"

**October**

- 6 Michael Hengartner, Ph.D.  
Staff Investigator, Genetics  
Cold Spring Harbor  
"Control of Programmed Cell Death (Apoptosis) in the Nematode *C. elegans*"
- 13 P. Andrew Futreal, Ph.D.  
Dept. Genetics & Surgery  
Duke University Medical Center  
"The BRCA1 and BRCA2 Cancer Susceptibility Genes: Where We Stand"
- 20 Harvey Preisler, M.D.  
Professor of Medicine  
Director, Rush Cancer Institute  
Chief Division of Hematology/Oncology  
"Regrowth Resistance as a Major Impediment to Successful Treatment Outcomes in Malignant Diseases"
- 27 Jay Harris, M.D.  
Clinical Director  
Professor of Radiation Oncology  
Harvard Joint Center for Radiation Oncology  
Beth Israel Hospital  
"Unresolved Issues in the Use of Breast Conserving Therapy"

**November**

- 3 Thomas J. MacVittie  
Vice President Biological Research  
Pro-Neuron, Inc.  
"The Rombopoietin/(Megakaryocyte) Growth and Development Factor: The Magic Bullet?"
- 10 Curt Civin, M.D.  
Professor of Oncology  
Johns Hopkins University  
"Purification and Expansion of Hematopoietic Stem Cells"

**November**

- 17 Kathleen Cho, M.D.  
Assistant Professor, Pathology and Oncology  
Joint Appointment, Gynecology and Obstetrics  
The Johns Hopkins University School of Medicine  
"The Molecular Pathogenesis of HPV-Associated Tumors of the Female Genital Tract"

The University of Michigan  
Comprehensive Cancer Center Grand Rounds

**December**

- 8 Allen S. Lichter, M.D.  
University of Michigan  
Radiation Oncology
- "Conformal Radiotherapy: A Decade  
of Clinical Experience"

**1996**

**January**

- 12 Eric Fearon, Ph.D.  
Associate Professor  
Human Genetics, Internal Medicine,  
Pathology  
University of Michigan
- "Genetics of Colorectal Cancer  
Biological Implications and Clinical  
Applications"
- 19 Ken Pienta, M.D.  
Associate Professor
- Jill Macoska, Ph.D.  
Assistant Professor
- Mark Day, Ph.D.  
Assistant Professor
- Surgery, Section of Urology  
University of Michigan
- "Research in Urologic Oncology"
- 26 Brian Athey, Ph.D.  
Research Investigator  
Anatomy and Cell Biology  
University of Michigan
- "Biomedical Diagnostic Imaging:  
The Challenge of Storage Retrieval  
Processing and Distribution"

**February**

- 2 Victor Strecher, Ph.D.  
Professor  
Health Behavior and Health Education  
University of Michigan
- "Advanced Communications  
Technology in Cancer Prevention"
- 9 Judith Karp, M.D.  
Program Director  
Chemoprevention Branch  
Div. Cancer Prevention and Control  
National Cancer Institute
- "Molecular Aspects of Cancer  
Prevention"
- 16 Warren S. Pear, M.D., Ph.D.  
Postdoctoral Fellow  
Massachusetts Institute of Technology
- "Novel Approaches for Understanding  
Hematopoietic Transformation"
- 23 David Markovitz, M.D.  
Associate Professor  
Internal Medicine  
University of Michigan
- "Regulation of HIV-2 Transcription by  
Human Cellular Factors"

The University of Michigan  
Comprehensive Cancer Center Grand Rounds

**March**

- |    |  |  |
|----|--|--|
| 1  | James Mulé, Ph.D.<br>Professor<br>Surgery<br>University of Michigan  | "Tumor Vaccines: A New Direction"  |
| 8  | Robert Martuza, M.D.<br>Professor and Chairman<br>Department of Neurosurgery<br>Georgetown University                | "Studies of Attenuated Multi-Mutated<br>Herpes Viruses for Cancer Treatment"                   |
| 15 | Avraham Raz, Ph.D.<br>Director, Metastasis Program<br>Michigan Cancer Foundation<br>Karmonos Cancer Institute        | "Autocrine Motility Factor Receptor:<br>From Basic to Clinic"                                  |
| 22 | Richard Gaynor, M.D.<br>Professor of Medicine and Microbiology<br>University of Texas Southwestern<br>Medical Center | "Regulation of Viral and Host<br>Polymerases by a Unique HIV-1<br>RNA Structural Element"      |
| 29 | Thomas J. Rosol, Ph.D.<br>Associate Professor<br>Department of Veterinary Biosciences<br>Ohio State University       | "The Role of Parathyroid Hormone-Related<br>Protein in Humoral Hypercalcemia of<br>Malignancy" |

**April**

- |    |  |  |
|----|--|--|
| 12 | Irving Weisman<br>Director of Laboratory Experimental Oncology<br>Professor of Immunology & Medicine<br>Department of Pathology<br>Stanford University | "Hematopoietic Stem Cells "  |
| 19 | David T. Curiel, M.D.<br>Director, Gene Therapy Program<br>University of Alabama at Birmingham   | "Targeted Tumor Eradication Mediated<br>by Single-Chain Antibody Directed Against<br>erbB-2" |
| 26 | Allen E. Bale, M.D.<br>DNA Diagnostics Laboratory<br>Department of Genetics<br>Yale University School of Medicine                                      | "Cancer and Birth Defects"   |

**May**

- |    |   |   |
|----|---|---|
| 3  | Frank J. Raushcer, III, Ph.D.<br>Associate Professor<br>Chair, Molecular Genetics Program<br>The WISTAR Institute         | "Zinc Finger Proteins in Development and<br>Disease: Studies on WT1 and BRCA-1" |
| 31 | Andrew Yeager, M.D.<br>Professor, Pediatric Hematology Oncology<br>Director of Bone Marrow Transplant<br>Emory University | "Bone Marrow Transplant"  |

Date: Wed, 24 Jul 96 13:22:24 EDT  
From: Ginny Schneider <ginnysch@p53.cancer.med.umich.edu>  
Reply to: Ginny Schneider <ginnysch@umich.edu>  
To: umccc.grandrounds@umich.edu, umccc.canbio@umich.edu  
Subject: Cancer Biology Seminar Schedule

Cancer Biology Seminars  
Fall 1996  
Wednesdays, 5:30 - 7:00 p.m.  
Sloan Dining Room

September 11 - Apoptosis and Cancer Therapy  
Max Wicha, MD, Internal Medicine  
Mike Clarke, MD, Internal Medicine

October 9 - Cancer Biology Training Program Postdocs  
Tracy Ram, PhD, Radiation Oncology  
Brian Ernsting, PhD, Biological Chemistry

November 13 - Special Guest Seminar  
Joseph R. Nevins, PhD  
Duke University

December 11 - Special Guest Seminar  
Charles J. Sherr  
St. Jude Children's Research Hospital

If you have any questions or need more information please contact  
Mike Imperiale, Ph.D. at imperial@umich.edu  
Thank you

Working Group Seminar on Statistical Methods for Cancer Research

Department of Biostatistics  
University of Michigan School of Public Health  
and  
Biostatistics Core  
University of Michigan Comprehensive Cancer Center

Room M4034 SPH II  
Mondays, 3:30-4:30 PM

Date	Speakers	Topic
FALL TERM		
September 30, 1996	KyungMann Kim	Basic Principles of ROC Analysis
October 14, 1996	Monica Kester	My summer internship at BMS
October 28, 1996	Myla Strawderman	Issues in Disease Screening
November 11, 1996	cancelled	
November 25, 1996	Dean Brenner Wade Schuette	Problems in image analysis
December 9, 1996	Daniel Normolle	Tumor growth in animal model: Part I
WINTER TERM		
January 13, 1997	KyungMann Kim	Design of cancer clinical trials
January 20, 1997	No seminar due to Martin Luther King day	
January 27, 1997	Songbai Wang	Continual Reassessment for Phase I trials
February 3, 1997	journal club	
February 10, 1997	Daniel Normolle	Tumor growth in animal model: Part II
February 17, 1997	journal club	
February 24, 1997	Fred Chang	
March 3, 1997	journal club	
March 10, 1997		
March 17, 1997	journal club	
March 24, 1997	No seminar due to ENAR meeting	
March 31, 1997	journal club	
April 7, 1997		
April 14, 1997	journal club	
April 21, 1997		
April 28, 1997	journal club	

Journal Club for Statistical Issues in Breast Cancer Research  
List of Articles to be Reviewed

Department of Biostatistics  
University of Michigan School of Public Health

Room M4034 SPH II  
Mondays, 3:30-4:30 PM

Winter Term 1996-1997

AUTHOR = Blumenson, Leslie E.  
AUTHOR = Bross, Irwin D. J.  
TITLE = A mathematical analysis of the growth and spread of breast cancer  
JOURNAL = Biometrics  
VOLUME = 25  
PAGES = 95-109  
YEAR = 1969  
KEYWORDS = Time dependence; Detection; Poisson distribution; Metastasis

AUTHOR = Oates, Richard P.  
TITLE = Forces of mortality among breast cancer patients  
JOURNAL = Journal of Chronic Diseases  
VOLUME = 29  
PAGES = 263-276  
YEAR = 1976  
KEYWORDS = Life table; Exposure model; Age matched survival curves; Competing risk

AUTHOR = Prentice, R. L.  
AUTHOR = Gloeckler, L. A.  
TITLE = Regression analysis of grouped survival data with application to breast cancer data  
JOURNAL = Biometrics  
VOLUME = 34  
PAGES = 57-67  
YEAR = 1978  
KEYWORDS = Proportional hazards regression; Censoring; Life tables; Log-rank test; Maximum likelihood estimation; Score test; Time dependence

AUTHOR = Shwartz, Michael  
TITLE = An analysis of the benefits of serial screening for breast cancer based upon a mathematical model of the disease  
JOURNAL = Cancer  
VOLUME = 41  
PAGES = 1550-1564  
YEAR = 1978  
KEYWORDS = Survival analysis

AUTHOR = Schwartz, M.  
TITLE = A mathematical model used to analyze breast cancer screening strategies (STMA V21 1863)  
JOURNAL = Operations Research, Journal of Operations Research Society of America  
VOLUME = 26  
PAGES = 937-955  
YEAR = 1978

AUTHOR = King, M.-C.  
AUTHOR = Lynch, H. T.  
AUTHOR = Selvin, S.  
TITLE = Laterality of breast cancer in families  
JOURNAL = American Journal of Epidemiology  
VOLUME = 110  
PAGES = 88-98

YEAR = 1979

AUTHOR = Tallis, G. M.  
AUTHOR = Leppard, P.  
AUTHOR = O'Neill, T. J.  
AUTHOR = Sarfaty, G.  
TITLE = The relationship of metastatic activity to primary tumor size with  
special reference to breast cancer  
JOURNAL = The Australian Journal of Statistics  
VOLUME = 21  
PAGES = 1-17  
YEAR = 1979

AUTHOR = Tallis, G. M.  
AUTHOR = O'Neill, T. J.  
AUTHOR = Leppard, P.  
AUTHOR = Sarfaty, G.  
TITLE = Screening for breast cancer  
JOURNAL = The Australian Journal of Statistics  
VOLUME = 22  
PAGES = 1-23  
YEAR = 1980

AUTHOR = Tallis, G. M.  
AUTHOR = O'Neill, T. J.  
TITLE = Analysis of detection processes for breast cancer  
JOURNAL = Biometrical Journal. Journal of Mathematical Methods in  
Biosciences.  
VOLUME = 23  
PAGES = 203-217  
YEAR = 1981  
KEYWORDS = Screening

AUTHOR = Dubin, Neil  
AUTHOR = Pasternack, Bernard S.  
TITLE = Case-control analysis of breast cancer in a screened population:  
Implications for the assessment of environmental exposure risk  
factors  
BOOK = Environmental Epidemiology: Risk Assessment  
PAGES = 154- 172  
YEAR = 1982

AUTHOR = Dubin, Neil  
TITLE = Effect of different mammographic radiation exposures on predicted  
benefits of screening for breast cancer  
JOURNAL = Statistics in Medicine  
VOLUME = 1  
PAGES = 15-24  
YEAR = 1982

AUTHOR = Pocock, Stuart J.  
AUTHOR = Gore, Sheila M.  
AUTHOR = Kerr, Gillian R.  
TITLE = Long term survival analysis: The curability of breast cancer  
JOURNAL = Statistics in Medicine  
VOLUME = 1  
PAGES = 93-104  
YEAR = 1982

AUTHOR = Gore, Sheila M.  
AUTHOR = Pocock, Stuart J.  
AUTHOR = Kerr, Gillian R.  
TITLE = Regression models and non-proportional hazards in the analysis of  
breast cancer survival  
JOURNAL = Applied Statistics  
VOLUME = 33



PAGES = 176-195  
YEAR = 1984  
KEYWORDS = Log-logistic regression; Logistic regression

AUTHOR = Taylor, Kathryn M.  
AUTHOR = Margolese, Richard G.  
AUTHOR = Soskoline, Colin L.  
TITLE = Physician's reasons for not entering eligible patients in a  
randomized clinical trial of surgery for breast cancer  
JOURNAL = New England Journal of Medicine  
VOLUME = 310  
PAGES = 1363-1367  
YEAR = 1984

AUTHOR = Moon, Thomas E.  
AUTHOR = Jones, Stephen E.  
AUTHOR = Bonaddona, Gianni  
AUTHOR = Powles, Trevor J.  
AUTHOR = Rivkin, Saul  
AUTHOR = Buzdar, Aman  
AUTHOR = Montague, Eleanor  
TITLE = Using a database of protocol studies to evaluate therapy: A breast  
cancer example (with discussion)  
JOURNAL = Statistics in Medicine  
VOLUME = 3  
PAGES = 333-339  
YEAR = 1984

AUTHOR = Clarkson, D. B.  
AUTHOR = Wolfson, D. B.  
TITLE = A displaced Poisson process applied to screening for breast cancer  
in stratified samples with false negatives  
JOURNAL = Statistica Neerlandica  
VOLUME = 39  
PAGES = 361-373  
YEAR = 1985  
KEYWORDS = Isotonic regression

AUTHOR = Day, N. E.  
AUTHOR = Walter, S. D.  
TITLE = Screening for cancer of the breast and cervix: Estimating the  
duration of the detectable preclinical phase  
BOOK = Modern Statistical Methods in Chronic Disease Epidemiology  
PAGES = 247- 258  
YEAR = 1986

AUTHOR = Klein, John P.  
AUTHOR = Keiding, Niels  
AUTHOR = Kamby, Claus  
TITLE = Semiparametric Marshall-Olkin models applied to the occurrence of  
metastases at multiple sites after breast cancer  
JOURNAL = Biometrics  
VOLUME = 45  
PAGES = 1073-1086  
YEAR = 1989  
KEYWORDS = Competing risks; Cox regression; Survival data

AUTHOR = Gong, Gail  
AUTHOR = Whittemore, Alice S.  
AUTHOR = Grosser, Stella  
TITLE = Censored survival data with misclassified covariates: A case study  
of breast-cancer mortality  
JOURNAL = Journal of the American Statistical Association  
VOLUME = 85  
PAGES = 20-28  
YEAR = 1990

KEYWORDS = Proportional hazards  
 AUTHOR = Marubini, E.  
 AUTHOR = Mezzanotte, G.  
 AUTHOR = Boracchi, P.  
 AUTHOR = Veronesi, U.  
 TITLE = Long term survival analysis: Breast cancer and age at diagnosis  
 JOURNAL = Statistics in Medicine  
 VOLUME = 9  
 PAGES = 737-748  
 YEAR = 1990

AUTHOR = Paci, Eugenio  
 AUTHOR = Duffy, Stephen W.  
 TITLE = Modelling the analysis of breast cancer screening programmes:  
 Sensitivity, lead time and predictive value in the Florence District  
 Programme (1975-1986)  
 JOURNAL = International Journal of Epidemiology  
 VOLUME = 20  
 PAGES = 852-858  
 YEAR = 1991

AUTHOR = Gray, Robert J.  
 TITLE = Flexible methods for analyzing survival data using splines, with  
 application to breast cancer prognosis  
 JOURNAL = Journal of the American Statistical Association  
 VOLUME = 87  
 PAGES = 942-951  
 YEAR = 1992  
 KEYWORDS = Censored data

AUTHOR = deSilva, C. J. S.  
 AUTHOR = Choong, P. L.  
 AUTHOR = Attikiouzel, Y.  
 TITLE = Artificial neural networks and breast cancer prognosis  
 JOURNAL = Australian Computer Journal  
 VOLUME = 26  
 PAGES = 78-81  
 YEAR = 1994

AUTHOR = Asselain, Bernard  
 AUTHOR = Fourquet, Alain  
 AUTHOR = Hoang, Thu  
 AUTHOR = Myasnikova, Catherine  
 AUTHOR = Yakovlev, Andrej  
 TITLE = Testing the independence of competing risks: An application to the  
 analysis of breast cancer recurrence  
 JOURNAL = Biometrical Journal. Journal of Mathematical Methods in  
 Biosciences.  
 VOLUME = 36  
 PAGES = 465-473  
 YEAR = 1994

AUTHOR = Floyd, Carey E., Jr  
 AUTHOR = Lo, Joseph Y.  
 AUTHOR = Yun, A. Joon  
 AUTHOR = Sullivan, Daniel C.  
 AUTHOR = Kornguth, Phyllis J.  
 TITLE = Prediction of breast cancer malignancy using an artificial neural  
 network  
 JOURNAL = Cancer  
 VOLUME = 74  
 PAGES = 2944-2948  
 YEAR = 1994

AUTHOR = Steinberg, Karen K.

AUTHOR = Smith, S. Jay  
AUTHOR = Thacker, Stephen B.  
AUTHOR = Stroup, Donna F.  
TITLE = Breast cancer risk and duration of estrogen use: The role of study  
design in meta-analysis  
JOURNAL = Epidemiology  
VOLUME = 5  
PAGES = 415-421  
YEAR = 1994

AUTHOR = Witte, John S.  
AUTHOR = Greenland, Sander  
AUTHOR = Haile, Robert W.  
AUTHOR = Bird, Cristy L.  
TITLE = Hierarchical regression analysis applied to a study of multiple  
dietary exposures and breast cancer  
JOURNAL = Epidemiology  
VOLUME = 5  
PAGES = 612-621  
YEAR = 1994  
KEYWORDS = Case control study

AUTHOR = Gail, Mitchell H.  
AUTHOR = Benichou, Jacques  
TITLE = Validation studies on a model for breast cancer risk (Corr: V86  
p803)  
JOURNAL = Journal of the National Cancer Institute  
VOLUME = 86  
PAGES = 573-575  
YEAR = 1994

AUTHOR = Sylvester, Richard  
AUTHOR = Bartelink, Harry  
AUTHOR = Rubens, Robert  
TITLE = A reversal of fortune: Practical problems in the monitoring and  
interpretation of an EORTC breast cancer trial  
JOURNAL = Statistics in Medicine  
VOLUME = 13  
PAGES = 1329-1335  
YEAR = 1994  
KEYWORDS = Stopping rule; Factorial design

## Appendix 2

1. A letter from Dr. Little about Mr. Chen's progress
2. A letter from Dr. Kim about Ms. Kester's progress
3. A letter from Dr. Lin about Mr. Zhang's progress



RODERICK J. LITTLE, PH.D.  
CHAIR, DEPARTMENT OF BIOSTATISTICS

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19 November, 1996

Dr. KyungMann Kim  
Department of Biostatistics  
University of Michigan  
Ann Arbor, MI 48109-2029

Dear KyungMann:

I am pleased to provide an assessment of Hua-Yun Chen's progress, in connection with the Training Grant for Biostatistics for Breast Cancer Research. Hua-Yun has successfully passed Part I and Part II of the Ph.D. Qualifying Examination, and is now developing ideas for a dissertation. We have now finalized a research article entitled "Proportional Hazards Regression with Missing Covariates", which was motivated by a data set involving breast cancer survival he analyzed while on the training grant. He is first author on this paper and did a great deal of the work himself. It has been submitted to the Student Competition for the Biometric Society Meetings in the Spring, and will be submitted to a statistics journal for review after some final editing. Hua-Yun's final thesis topic will involve topics in the analysis of biomedical data with missing values, which will also have application to Breast Cancer research studies. Hua-Yun continues to take classes and gain excellent grades, with a cumulative GPA of 7.6. He shows every indication of being one of the truly outstanding Ph.D. students that our Department has produced.

I might also comment in passing that I am on the dissertation committee of Daowen Zhang, another of our students who was previously on the training grant. Daowen is working with Xihong Lin on analysis of repeated-measures data via nonlinear models, developing new techniques that also have application to repeated measurements of outcomes in breast cancer trials. I have just seen his dissertation proposal and it is exceptionally substantial and well written. I have little doubt that he will also be an outstanding Ph.D. graduate who will be a great credit to the Training Grant.

Thank you for providing me with the opportunity to comment on these fine students.

Sincerely,

Roderick J. Little



Comprehensive  
Cancer Center

University  
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107 Simpson Drive  
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(313) 936-7506  
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BIostatISTICS

November 27, 1996

To whom it may concern:

This letter is to provide an assessment of Ms. Monica Kester's progress on the Training Program in Biostatistics for Breast Cancer Research awarded to the Department of Biostatistics of the University of Michigan School of Public Health.

Initially as Biostatistics faculty and director of Biostatistics at the Cancer Center, I have been providing mentorship to Ms. Kester for the Training Program in Biostatistics for Breast Cancer Research. She was interested in one of the breast cancer cognate area, "Preventive and Therapeutic Clinical Trials". Beside taking relevant and required courses in Biostatistics and a course in Epidemiology, she has been sitting in on consulting sessions by myself and Ms. Myla Strawderman, staff statistician for the Biostatistics Core of the Cancer Center. Because of her keen interest in clinical trials, the Biostatistics Core of the Cancer Center provided a partial funding for her to attend the Annual Meeting of the Society for Clinical Trials in Pittsburgh, Pennsylvania in May of 1995. During the Summer of 1995, she worked as intern at Bristol-Myers Squibb in Wallingford, Connecticut on a cancer clinical trial project applying diagnostic procedures for Cox proportional hazards regression modeling. In the Fall Term she gave a presentation of her work at BMS at the Statistical Methods in Cancer Research seminar. Currently she is mostly taking required courses in biostatistics and cognate courses in public health genetics. In the 1995-1996 academic year, her GPA was excellent with 7.78 out of 8. Recently she started to work on a very exciting and interesting medical resonance imaging project for breast cancer under the mentorship of Dr. Thomas Chenevert and myself. Dr. Chenevert's MRI project is funded by the Department of Defense Breast Cancer Research Program.

Sincerely,

KyungMann Kim, Ph.D.  
Associate Professor  
and Director of Biostatistics

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Center Designated by the  
National Cancer Institute

A Member of the  
National Comprehensive  
Cancer Network



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Xihong Lin  
Department of Biostatistics  
(313) 936-1012, FAX (313) 763-2215

November 23, 1996

To whom it may concern:

Daowen Zhang was supported as a trainee by the Breast Cancer training grant last year. As Daowen's Ph.D. thesis advisor, I would be glad to describe how important and useful this one-year trainee experience is in terms of helping him identify his dissertation topic and how his dissertation work is related to breast cancer research.

Longitudinal data and familial data are common in many breast cancer studies. A common feature of such data is that observations are likely to be correlated. For examples, in longitudinal studies, repeated observations obtained over time from the same subject are likely to be correlated; in familial studies, observations from family members within the same family are likely to be correlated, since they share the same genetic and environmental factors. Familial studies are particularly useful in breast cancer research, since it is known that genetic factors may play an important role in developing breast cancer and it is important to study the familial aggregation of breast cancer using familial data.

However, analyses of longitudinal data and familial data are often difficult, since a valid statistical inference needs to account for correlation between outcomes, and the relationship between the outcome variable and the explanatory variables may often be complicated. Daowen's one-year trainee experience provided him an excellent opportunity to recognize the importance of these statistical issues involved in breast cancer research and also provided him a better understanding of the biological process of this disease. His current dissertation work is to develop a new class of statistical models, generalized additive mixed models (GAMMs), which are very useful for analyzing longitudinal and familial data. This is because GAMMs account for correlation between observations using random effects and use nonparametric regression to allow complicated relationships between the outcome variable and the explanatory variables. Another important feature of GAMMs is that they allows us to test for familial aggregation of breast cancer using familial data.

We plan to apply our new models to a four-year multi-center longitudinal study on breast cancer survivors (BCS), which is currently under review by the U.S. Army Research Institute. Professor MaryFran Sowers in the Department of Epidemiology at the University of Michigan





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serves as the principle investigator and I am the principle biostatistician on the grant. Major objectives of this study are to compare various clinical and biological features between BCS who have undergone surgery with BCS who have had chemotherapy. For example, we are interested in studying the treatment effect on the risk of ovarian failure, menopausal symptoms, annual bone density loss, and levels of free estradiol and FSH. Daowen will help us with the analysis of the data. I am glad that he has gained some experience in breast cancer research during his one-year traineeship last year. This experience will definitely help him make more contribution to this project and communicate better with the epidemiologists and physicians on this project.

I would be glad to provide any further information on Daowen's work if necessary. Thank you very much for your consideration.

Sincerely,

Xihong Lin, Ph.D.  
Assistant Professor

T E E A

### Appendix 3

1. An updated summary of activities of Mr. Chen
2. An updated summary of activities of Ms. Kester
3. An updated summary of activities of Mr. Zhang

# Trainings on Breast Cancer Research

Hua Yun Chen

During 1995-1996 academic year, I obtained trainings on the following aspects that directly related to the breast cancer research.

## 1. Research

I was working on the analysis of the data from one breast cancer research project. The objective of the research was to evaluate the effects of diagnostic factors, disease status, and different treatment regimes on the survival of breast cancer patients. Some of the measurements were missing for part of the patients. This presents difficulties when we try to adjust the effect of a measurement of interest. To solve this problem, I investigated the possibility to do the adjustment when the covariates are not observed for all the patients in the Cox regression model.

## 2. Seminar attendance

I attended the regular breast cancer surgeon meetings of the Department of surgery at the University of Michigan hospital. In these meetings, either the clinically difficult cases related to breast cancer were discussed with regard to diagnosis and surgery, or special guests were invited to present the recent advances on breast cancer researches. The identification of the gene related to the breast cancer and the clinical decision making were among the topics. These discussions enriched my knowledge on both the complex of breast cancer researches and the impacts of the prevalence of breast cancer on individual, family, and society. I also attended the Cancer Center grand round seminars. Topics on different aspects of Cancer researches were presented. As a branch of the general cancer researches, the breast cancer research has the common difficulties as well as its special problems. This seminar series gave us a overview of the general cancer researches which helped us to understand the nature and needs of the breast cancer research.

## 3. Course work

I took several statistical courses to fulfill the requirements of the Ph.D program at the Biostatistics Department. Most of the courses discussed the statistical methods that related to cancer researches, such as sequential methods for clinical trial data, random effect model for follow-up data, imputation methods for longitudinal attrition data, to name a few. I also took courses on related fields, for example, *Nutrition* from the Epidemiology Department. During the study of this course, I reviewed the papers extensively on the nutritional factors, especially, dietary fat on the breast cancer morbidity. I wrote a report to summarize the researches on this aspect and discuss the problem whether a conclusion could be reached in regards to the existing results or more researches were needed in regards to the existing research methods. The courses

T . . .

taken during the last academic year enable me to fulfill the course work requirements for the Ph.D program at the Biostatistics Department. Consequently, I was advanced to candidacy after other requirements were met in the fall.

# Summary of Activities

Monica Kester

November 25, 1996

Much of my breast cancer training has involved the required course work in the Department of Biostatistics. I have completed many courses which will be indispensable as I continue to explore the realm of breast cancer research. My academic training has included the following courses which were offered through the University of Michigan Department of Biostatistics: Probability and Distribution Theory, Applied Regression Analysis, Analysis of Variance, Stochastic Processes, Statistical Inference, and Survival Time Analysis. The knowledge I gained in the Survival Time Analysis course has been especially useful in my cancer related research. Currently my course work continues and includes Categorical Data Analysis, Design of Experiments, Fundamentals of Survey Sampling, and An Introduction to Genetics in Public Health.

In addition, I participated in statistical consulting sessions at the University of Michigan Comprehensive Cancer Center. These opportunities have been extremely helpful as I learn how statisticians and clinicians interact on important projects. Before attending these meetings it was difficult for me to envision what types of problems might arise due to limitations in the data. These consulting sessions have helped me to learn to deal with these limitations and have guided me toward formulating important, relevant questions as I begin to work on my own projects.

My training has also included attending a conference for the Society of Clinical Trials in May of 1996. The conference proved to be extremely instructional as far as understanding what problems are frequently faced in the clinical trials setting and what types of solutions have been proposed to resolve these problems. For example, I was introduced to some of the difficulties in the area of data management. When I encountered similar problems in my own work, I realized that I had gained a wealth of knowledge from the

## New Trainee Activities

*Mr. Tang have been working on Dr. Pierce's project with mentorship from Drs. Kim and Pierce. Ms. Kester have been working on Dr. Chenevert's project with mentorship from Drs. Chenevert and Kim. Mr. Mukherjee has begun to work with Dr. Chang, former Steering Committee member, and Dr. John Ingold from William Beaumont Hospital in Royal Oak, Michigan on analysis of a breast cancer database of over 1,500 patients who were surgically operated on by Dr. Ingold with mentorship from Dr. Kim.*

## New Initiatives

The most significant new initiatives is the plan to supplement trainees' stipend level from the current 35% to the regular 50% with partial funding from the UMCCC Biostatistics Core grant. This supplement in stipend will require trainees to actually work as a part time graduate student research assistants in the Biostatistics Core. The trainees will work on relevant breast cancer research projects with supervision of the UMCCC statisticians in the Biostatistics Core.

With the Fall term, there *has been* a biweekly working group seminar series in "Statistical Methods for Cancer Research". This will be used as a forum to visit new statistical research initiatives for breast cancer research in particular and for cancer research in general. *With the Winter term, this biweekly seminar series will alternate with a journal club on statistical issues in breast cancer research. The partial list of articles to be reviewed in the journal club is attached in Appendix 1.*

## CONCLUSIONS

The training program is maturing nicely with a meaningful progress, despite loss of two excellent trainees as we *have recruited* three new talented trainees for the third year of the grant. Especially, all three and the soon-to-be-fourth trainees are lot more committed toward biostatistics for breast cancer research. In the future, this training program will play a more active important role in the further expansion and development of Biostatistical training and research activities in the Biostatistics Department.

Eventually we plan to develop a training program in biostatistics for cancer research for submission to the National Cancer Institute when the current training program from the Department of Defense terminates.

discussions at this conference and I was able to sort through the difficulties myself.

During the summer of 1996 I worked as an intern in the Department of Biostatistics and Data Management at Bristol-Myers Squibb. Working in the Biostatistics Oncology Division, I implemented techniques for testing proportional hazard assumptions in the Cox regression model. The tools I developed in my course work allowed me to succeed in this endeavor. The techniques with which I worked are directly applicable to breast cancer research involving survival time data analysis.

Upon my return to the University of Michigan, I presented the techniques I explored during the previous summer to the biostatistics division of the University of Michigan Comprehensive Cancer Center and to interested clinicians. This presentation took place at our biweekly lecture series, Statistical Methods in Cancer Research, during which speakers discuss current developments in cancer research. These seminars are extremely useful in allowing trainees to become familiar with cutting edge developments in breast cancer research.

Currently, I am working on a very interesting project through the cancer center. The objective of the study is to determine the diagnostic power of a new MRI technique. The basic process is to inject contrast material into women for whom a breast abnormality has been detected. Cross sectional images of the breast are then taken using the new MRI technique. My involvement entails performing a statistical analysis on the data which has been collected. Hopefully, this technique will provide an alternate method of assessing if breast abnormalities are malignant. There are some interesting issues pertaining to nonlinear statistical modeling which I have encountered while working on this study. In addition, there are statistical issues involved in imaging which I am sure will prove to be both exciting and challenging.



# Breast Cancer Training Activity Report

Daowen Zhang

I was in the Breast Cancer Training Grant from January 1995 to April 1996. The following is the summary of the activities I was involved:

- **Breast Cancer Seminar Attendance:** I attended a series of breast cancer seminars held in the medical school, the University of Michigan. In those seminars, researchers on breast cancer presented some cases that are difficult to diagnose or treat; or investigators reported their latest findings on breast cancer; or physicians in the breast cancer related areas were invited to present their experience in treating breast cancer patients. We, as breast cancer trainees, attended these seminars to get first hand experience about breast cancer research, to further understand the importance of breast cancer research, and to identify potential statistical problems arising in such research.
- **Projects Involved:** When I was in the Breast Cancer Training Grant, I was involved in some breast cancer related projects. A typical one was the project to examine the survival experience for patients with locally advanced breast cancer after multimodal therapy, conducted by Drs. Merajver and Pierce in the Departments of Internal Medicine, Radiation Oncology, the University of Michigan. I worked as a biostatistician in the project, and was involved from error-checking the raw data to performing statistical analyses and writing reports for the interpretation of the results.
- **Course Works:** During the time period I was in the Breast Cancer Training Grant, I took some biostatistical and epidemiological courses that are potentially useful for breast cancer research: *Statistical Analysis with Missing Data*, *Time Series Analysis*, *Longitudinal Analysis for Epidemiological Studies*, *Sequential Methods for Clinical Trials*.
- **Methodological Research:** My research interest is in modeling correlated continuous and discrete data, which are frequently arising in breast cancer research. For example, any breast cancer research involves following up patients, in which the data from a same patient are usually time-varying and positively correlated. I developed some methodology for longitudinal data with censored outcome or censored covariates. Now under the guidance of my advisors, Drs. Xihong Lin and Jonathan Raz, I am developing some theory and software to make semiparametric inference for longitudinal data where the interest is in the time trend as well as covariate effects.